General

Guideline Title

Optimal use recommendations for atypical antipsychotics: combination and high-dose treatment strategies in adolescents and adults with schizophrenia.

Bibliographic Source(s)

Canadian Agency for Drugs and Technologies in Health (CADTH). Optimal use recommendations for atypical antipsychotics: combination and high-dose treatment strategies in adolescents and adults with schizophrenia. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2011 Dec. 30 p. [50 references]

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 10, 2016 – Olanzapine : The U.S. Food and Drug Administration (FDA) is warning that the antipsychotic medicine olanzapine can cause a rare but serious skin reaction that can progress to affect other parts of the body. FDA is adding a new warning to the drug labels for all olanzapine-containing products that describes this severe condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Recommendations

Major Recommendations

Optimal Use Recommendation 1: Clozapine Combinations versus Monotherapy

The Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee (CERC) recommends that clozapine-based antipsychotic combination therapy should not be used for patients with schizophrenia who inadequately respond to standard-dose clozapine monotherapy.* (*Voting: agree 9; disagree 0*)

*The available data for combination therapy with clozapine were primarily for oral risperidone, with some evidence available for aripiprazole and sulpiride. There was no evidence available for other atypical antipsychotic agents.

Underlying Values and Preferences

When developing this recommendation, CERC placed a high value on:

- The few significant differences in clinical efficacy between clozapine-based antipsychotic combination therapy and standard-dose clozapine monotherapy, and the lack of consistent evidence
- Safety concerns of augmenting clozapine treatment with an additional antipsychotic agent

CERC also considered:

- The higher cost of adding another antipsychotic agent to clozapine

Context

- With respect to the available evidence for this comparison, four CERC members considered the evidence to be of low quality, three of moderate quality, and one of high quality. The evidence pool consisted of 12 randomized controlled trials (RCTs; presented in 13 articles) with three rated as being of good quality using the Scottish Intercollegiate Guidelines Network (SIGN-50) rating scheme. Most studies tended to be short term and underpowered for clinically relevant outcomes.
- No clinically important benefits were seen with combination therapy, and there may be an increase in serious adverse effects and costs. A statistically significantly increased risk of serious adverse events was found with clozapine combination therapy compared with clozapine monotherapy. In the case of clozapine combined with risperidone, harms such as sinus tachycardia, severe psychotic disorder, and severe hallucinations were more prevalent in comparison with clozapine monotherapy.
- Despite not being recommended, for those patients who *are* initiated on clozapine-based combination therapy, clinical opinion suggests that efficacy should be evaluated after an adequate trial using therapeutic doses up to the maximum recommended doses. If no improvement is observed or adverse events become apparent, clozapine-based combination therapy should be discontinued.
- There was no RCT evidence available examining clozapine-based combination therapy involving more than two agents. Clinical opinion suggests that the risk of adverse events increases significantly as the number of antipsychotic agents used in combination increases.

Optimal Use Recommendation 2: Combination Therapy with Non-clozapine Atypical Antipsychotic Agents versus Monotherapy

CERC recommends that non–clozapine-based atypical antipsychotic combination therapy should not be used for patients with schizophrenia who inadequately respond to a standard-dose atypical antipsychotic agent.* (*Voting: agree 9; disagree 0*)

*Evidence was only available for the combination of risperidone or quetiapine with aripiprazole. There was no evidence for other combinations involving atypical antipsychotic agents.

Underlying Values and Preferences

When developing this recommendation, CERC placed a high value on:

- Safety concerns of augmenting atypical antipsychotic treatment with an additional antipsychotic agent
- The potentially higher cost of non–clozapine-based combination therapy in comparison with standard-dose monotherapy

CERC also considered:

- The few significant differences in clinical efficacy between non–clozapine-based antipsychotic combination therapy and standard-dose non-clozapine monotherapy

Context

- Evidence was very limited for this comparison, as only one RCT was identified; all CERC members agreed that the available evidence was of low quality.
- Although the evidence from the single RCT did not indicate that combination antipsychotic therapy was associated with a higher risk of adverse effects than monotherapy, clinical experience and non-RCT evidence outside the scope of the Canadian Agency for Drugs and Technologies in Health (CADTH) review suggests that there are increased adverse effects associated with non–clozapine-based antipsychotic combination therapy.

Optimal Use Recommendation 3: Standard-Dose Clozapine versus High-Dose Non-clozapine Atypical Antipsychotic Agents

CERC recommends that standard-dose clozapine should be used instead of high doses of other atypical antipsychotic agents for patients with schizophrenia who inadequately respond to a standard-dose atypical antipsychotic agent.* (*Voting: agree 8; disagree 1*)

*Evidence was only available for use of high-dose risperidone and high-dose olanzapine. There were no studies comparing other atypical antipsychotic agents used at high doses with standard-dose clozapine. Of note, the threshold for defining high-dose olanzapine in the CADTH systematic review was higher than Health Canada–approved doses.

Underlying Values and Preferences

When developing this recommendation, CERC considered:

- Safety concerns related to use of high-dose risperidone or olanzapine compared with standard-dose clozapine, despite the lack of clear differences in safety profile between treatments in the available studies
- Clinical experience grounded in evidence beyond the scope of the CADTH systematic review indicating the higher efficacy of clozapine compared with other antipsychotic agents in the management of patients with treatment-resistant schizophrenia
- The inconsistent differences in clinical efficacy between high-dose risperidone and standard-dose clozapine, and the lack of consistent clinical evidence
- The fact that the cost of clozapine is higher than that of (generic) risperidone and other atypical antipsychotic agents used at high doses

Context

- All CERC members rated the evidence as being of low quality. The evidence pool for risperidone consisted of three RCTS; most were of short duration, and none were considered to be of high quality based on the SIGN-50 rating scheme. In terms of efficacy outcomes, standard-dose clozapine was statistically superior to high-dose risperidone for Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression — Severity (CGI-S), extrapyramidal effects, and level of function (Global Assessment of Functioning scale [GAF]); however, there was no difference in terms of Positive and Negative Syndrome Scale (PANSS) or response rates. In terms of harms, high-dose risperidone was statistically superior in terms of Parkinsonism and weight. The clinical significance of these differences is uncertain.
- The evidence for olanzapine consisted of five RCTs, none of which were considered to be of high quality, based on the SIGN-50 instrument. There were no statistically significant differences in efficacy outcomes between high-dose olanzapine and standard-dose clozapine. However, high-dose olanzapine was associated with a lower risk of withdrawal due to adverse events.
- It was unclear whether patients included in the available RCTs had previously achieved partial response on standard doses of antipsychotic agents. Furthermore, not all studies reported the number of antipsychotic agents that were previously tried. CERC noted that most patients who have failed more than two agents in clinical practice move to standard-dose clozapine as the next treatment strategy.
- In some of the included studies, the daily dose of clozapine was considered suboptimal (<350 mg per day). However, comparison of trials with suboptimal clozapine dosing versus adequate dosing did not reveal a systematic difference in results. In the subgroup analysis of trials with mean clozapine doses above 350 mg per day, there were no significant differences in efficacy between clozapine and high-dose strategies, and a non-statistically significant trend toward more withdrawals due to adverse events in the clozapine arm.
- The CADTH review considered risperidone doses over 6 mg per day as high dose (based on expert opinion), while Health Canada has approved doses up to and including 12 mg per day. The average dose for risperidone in the included trials for this comparison was approximately 8 mg per day. For olanzapine, doses above 20 mg per day (the Health Canada–approved maximum recommended dose) were considered high in the CADTH review; the average dose in the included trials was approximately 32 mg per day.
- The daily cost of clozapine is higher than high-dose risperidone. The cost-effectiveness of clozapine compared with high-dose strategies is uncertain, as there was insufficient evidence on rehospitalizations and other clinically relevant outcomes related to health care utilization.
- Based on the available evidence (outside the scope of the CADTH review) demonstrating the higher efficacy of clozapine compared with standard doses of other antipsychotic agents, most, but not all, CERC members considered standard-dose clozapine to represent the standard of care for patients with treatment-resistant schizophrenia. Although there were few statistically significant differences favouring clozapine over high-dose risperidone or olanzapine in the CADTH review, this evidence was considered insufficient to support the use of high-dose atypical antipsychotic agents in place of clozapine.

Optimal Use Recommendation 4: Standard-Dose versus High-Dose Non-clozapine Atypical Antipsychotic Agents

CERC recommends that high doses of a (non-clozapine) atypical antipsychotic agent not be used instead of standard doses in patients with schizophrenia who inadequately respond to a standard-dose antipsychotic agent.* (*Voting: agree 9; disagree 0*)

*Evidence was available only for use of high-dose risperidone and high-dose quetiapine. There were no studies comparing other atypical antipsychotic agents used at high doses with standard-dose (non-clozapine) antipsychotic therapy. Of note, the threshold for defining high-dose

quetiapine in the CADTH systematic review was higher than Health Canada–approved doses.

Underlying Values and Preferences

When developing this recommendation, CERC placed a high value on:

- The few significant differences in clinical efficacy between high-dose risperidone or quetiapine and standard-dose atypical antipsychotics, and the lack of consistent evidence
- Safety concerns regarding using high-dose antipsychotic therapy
- The higher costs of high-dose antipsychotics in comparison with standard doses

Context

- In the CADTH systematic review, studies comparing high-dose atypical psychotics with typical antipsychotic agents were included regardless of the dose of the typical antipsychotic. The typical antipsychotics used as comparator in the identified trials were haloperidol and chlorpromazine. Based on clinical opinion, CERC considered haloperidol 10 mg and chlorpromazine 1,000 mg to be the maximum daily doses in clinical practice; studies that used higher doses were not considered. Hence, the evidence considered by CERC in developing this recommendation consisted of one study comparing high-dose risperidone with haloperidol 10 mg per day, and one study comparing high-dose quetiapine with standard-dose quetiapine.
- Eight CERC members considered the quality of evidence to be of low quality, and one, moderate quality. Neither of the included studies was rated as being of high quality according to the SIGN-50 rating scheme. There was a lack of evidence for many clinically important endpoints such as relapse, hospitalizations, mortality, functional capacity, and clinical remission.
- It was unclear whether patients included in the available RCTs had previously achieved partial response on standard doses of antipsychotic agents.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Schizophrenia or schizoaffective disorder

Guideline Category

Management

Treatment

Clinical Specialty

Family Practice

Pediatrics

Pharmacology

Psychiatry

Intended Users

Advanced Practice Nurses

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Pharmacists

Physician Assistants

Physicians

Public Health Departments

Utilization Management

Guideline Objective(s)

To provide recommendations for the optimal prescribing and use of atypical antipsychotic (also known as "second-generation antipsychotic" or "SGA") combination and high-dose treatment strategies in adolescents and adults with schizophrenia or schizoaffective disorder inadequately controlled on standard-dose antipsychotic monotherapy

Target Population

Adolescents and adults with schizophrenia or schizoaffective disorder

Interventions and Practices Considered

1. Clozapine-based combination therapy (not recommended)
2. Non–clozapine-based atypical antipsychotic (AAP) combination therapy (not recommended)
3. Standard-dose clozapine versus high-dose non-clozapine AAP agents
4. High doses of a (non-clozapine) AAP agent (not recommended)

Note: The antipsychotic agents considered were aripiprazole, asenapine, clozapine, olanzapine, iloperidone, paliperidone, quetiapine, risperidone, and ziprasidone.

Major Outcomes Considered

- Efficacy outcomes
  - Positive and Negative Syndrome Scale (PANSS) (total, positive, negative score)
  - Brief Psychiatric Rating Scale (BPRS)
  - Clinical Global Impression — Improvement scale (CGI-I) and Severity scale (CGI-S)
  - Response rate
  - Relapse rate
  - Clinical remission
  - Functional capacity
  - Quality of life
  - Persistence with therapy
- Harms
  - Barnes Akathisia Rating Scale (BARS)
  - Abnormal Involuntary Movement scale (AIMS)

- Simpson-Angus Scale (SAS)
- Extrapyramidal symptoms
- Cognitive impairment
- All-cause mortality
- Suicidality
- Cardiovascular events
- Incident diabetes
- Prolactinemia
- Hemoglobin A1C
- Fasting plasma glucose
- Lipid profile (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides)
- Agranulocytosis
- Serious/severe adverse events
- Withdrawals due to adverse events
- Hospitalization

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The clinical evidence for the use of atypical antipsychotic (AAP) combination and high-dose treatment strategies in adolescents and adults with schizophrenia inadequately controlled on standard-dose monotherapy was derived from the Canadian Agency For Drugs and Technologies in Health (CADTH) Optimal Use Report: *A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia* (see the "Availability of Companion Documents" field).

Research Questions

The objective of the systematic review was to identify and appraise the clinical evidence pertaining to use of AAP combination therapy and high-dose treatment strategies in adolescents and adults with schizophrenia. The research questions were:

1. What is the comparative clinical effectiveness (including clinical benefits and harms) of using combination therapy with AAPs (including the use of another AAP or a typical antipsychotic [TAP] as the other agent) compared with AAP monotherapy for the treatment of adolescents and adults with schizophrenia for whom treatment with a single AAP or TAP at recommended doses is inadequate?
2. What is the comparative clinical effectiveness (including clinical benefits and harms) of using high-dose AAP therapy compared with standard dose AAP therapy for the treatment of adolescents and adults with schizophrenia for whom treatment with an AAP or TAP at recommended doses is inadequate?

Literature Search Methods

When possible, the CADTH builds on existing applicable Canadian and international initiatives and research. The first phase of the research process was to conduct a literature search for existing systematic reviews or guidance on AAP combination and high-dose use. National Institute for Health and Clinical Excellence guidelines (2009), a Drug Effectiveness Review Project report (2010), Canadian Psychiatric Association guidelines (2004), American Psychological Association guidelines (2004 and 2009), and other systematic reviews on AAP combination therapy and on high-dose AAPs were identified and assessed. None of these reports sufficiently addressed the tabled research questions; therefore, a systematic review of the primary literature was conducted.

The methodology for the systematic review is presented in detail in the project protocol (see the "Availability of Companion Documents" field). The full literature search strategy is presented in Appendix 1 of the systematic review (see the "Availability of Companion Documents" field). The following databases were searched via the OVID interface: MEDLINE (1950–), MEDLINE In-Process & Other Non-Indexed Citations, EMBASE (1980–), PsycINFO (1967–), and The Cochrane Central Register of Controlled Trials. A parallel search was run in the CINAHL database via EBSCO. PubMed was also searched to capture additional citations not found in MEDLINE. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were each AAP drug name plus more general terms (e.g., atypical antipsychotics, second-generation antipsychotics), schizophrenia, schizoaffective disorder, drug combinations, and drug dosage. Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs) or controlled clinical trials. Retrieval was not limited by publication year, but was limited to the English or French language. The Internet was searched to identify unpublished (grey) literature from websites and databases of health professional associations, health technology assessment agencies, and related entities. Bibliographies of selected studies were also reviewed. Literature alerts were monitored after completion of the primary search in June 2010. Studies published after June 2010 that met the inclusion criteria were not included in meta-analyses; however, sensitivity analyses were performed to ensure results were not significantly changed (data not reported). Manufacturers of the agents considered in this review were provided the opportunity to submit unpublished data.

Studies were selected independently by two reviewers based on criteria developed a priori, with discrepancies resolved through consensus, or the judgment of a third reviewer if agreement could not be reached.

Selection Criteria

Studies were included if they met all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria

Population: Adolescents (13 to 17 years old) or adults (≥ 18 years old) with schizophrenia or schizoaffective disorder (including the first episode of schizophrenia, acute phase, or chronic phase) inadequately controlled with one or more antipsychotic (atypical or typical) monotherapy regimens.

Interventions: 1) Combinations consisting of one of the AAPs listed under "Interventions and Practices Considered" field, at a dose lower than or equal to the definition of high dose, with one or more other antipsychotic drugs (atypical or typical); or 2) AAP monotherapy at high doses. High dose was defined for each AAP based on Health Canada approved doses and input from clinical experts.

Comparators: AAP or TAP monotherapy at any dose; combinations of antipsychotic drugs at any dose.

Outcomes: Symptoms of schizophrenia (Positive and Negative Syndrome Scale [PANSS], Brief Psychiatric Rating Scale [BPRS], Clinical Global Impression — Improvement [CGI-I], Clinical Global Impression — Severity [CGI-S]), response rate, cognition, withdrawals, and serious adverse events.

Study Design: Randomized controlled trials (RCTs) (including parallel, crossover, placebo- or active-controlled).

Exclusion Criteria

- Studies of mixed populations with more than 15% of participants not diagnosed with schizophrenia or schizoaffective disorder, and/or no subgroup analysis reported for patients with schizophrenia or schizoaffective disorder
- Studies on first episode psychosis that is not specified as first episode schizophrenia
- Studies on schizophreniform disorder
- Studies on monotherapy comparisons between different AAPs, different TAPs, or between AAP and TAP at doses lower than the pre-defined high-dose thresholds
- Studies comparing TAP monotherapy at a recommended dose with the same TAP at high dose
- Studies comparing TAP monotherapy at a recommended dose with a combination of the same or different TAP plus another antipsychotic
- Studies on combination therapy with an antipsychotic agent and non-antipsychotic agent (e.g., mood stabilizer)
- Studies published in languages other than French or English

Selection of Primary Studies

Figure 1 in the systematic review illustrates the selection process used to identify primary studies. After removal of duplicates, a total of 2,824 citations were identified in the literature search. Of these, 2,599 citations were excluded, based on titles and/or abstracts. These consisted mainly of reviews, study designs other than RCTs, and studies in which comparators were not of interest. Full-text articles of the remaining 225 citations were assessed, and 41 articles representing 30 unique RCTs were included in the systematic review. The complete lists of included and excluded studies are presented in Appendices 6 and 7 of the systematic review, respectively. In several instances, data from the same clinical trial were

presented in multiple articles; these are outlined in Appendix 8 of the systematic review. The publication with the longest duration of follow-up was used when analyzing data from such trials. Data from 19 articles describing 18 RCTs were included in the meta-analyses. A summary of studies not included in the reference case meta-analyses is presented in Appendix 18 of the systematic review.

Number of Source Documents

41 articles (3 abstracts, 1 letter to editor, 37 full text) describing 30 studies were included in the qualitative synthesis.

19 articles describing 18 randomized controlled trials were included in the reference case meta-analyses.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

For each recommendation, the available evidence was rated as "high," "moderate," and "low." This rating was based on an assessment of evidence quality across all outcomes considered "important" or "critical" by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee (CERC).

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The clinical evidence for the use of atypical antipsychotic (AAP) combination and high-dose treatment strategies in adolescents and adults with schizophrenia inadequately controlled on standard-dose monotherapy was derived from the Canadian Agency For Drugs and Technologies in Health (CADTH) Optimal Use Report: *A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia* (see the "Availability of Companion Documents" field).

Quality Assessment and Data Extraction

Study quality was assessed using the Scottish Intercollegiate Guidelines Network (SIGN-50) checklist for randomized controlled trials. Quality assessment was performed by one reviewer and verified by a second reviewer. Disagreements were resolved through consensus, or the judgment of a third reviewer if agreement could not be reached.

Data were extracted from included studies using templates designed a priori. Data were abstracted by one reviewer with verification by a second reviewer. Disagreements were resolved through consensus, or the judgment of a third reviewer if agreement could not be reached.

Data Synthesis and Analysis

Some included studies administered antipsychotic agents at fixed doses, while others allowed dose titration. Antipsychotic dosing was reported variably in the included trials that permitted dose titration: average dose during the study, mean endpoint dose, and median endpoint dose. Mean endpoint doses are reported in the systematic review where available; otherwise, median endpoint values are reported. Average doses were considered only if no measure of endpoint dose was reported.

For continuous outcome measures, meta-analysis was performed using a random effects generic inverse variance approach. Mean differences from baseline to follow-up (with corresponding measures of uncertainty), or variations thereof, were abstracted for each treatment arm from all included studies for all continuous outcome measures of interest. Where standard deviations for change scores were not reported, standard deviations were imputed where possible.

Dichotomous outcomes, such as serious adverse events and suicidality, were meta-analyzed using relative risk as the effect measure. Dichotomous

categories were defined as "no event" or "one or more events."

The degree of heterogeneity in meta-analyses was estimated using the I^2 statistic. Where heterogeneity was greater than 75%, pooled results were not presented. Selected forest plots are presented in Appendix 4 of the systematic review (see the "Availability of Companion Documents" field).

Subgroup analyses were performed, where possible, according to individual atypical antipsychotics and by number of antipsychotic drugs failed prior to the trial (i.e., ≥1, ≥2). Individual sensitivity analyses were conducted by including studies in adolescents, or by removing:

- Studies of poor quality
- Studies employing a crossover design
- Studies of less than three months' duration
- Studies in which intention to treat (ITT) results were not reported
- Studies that examined agents not currently available in Canada
- Studies with clozapine dose less than 350 mg per day
- Studies reported only in conference/symposium abstracts

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Project Overview

Key steps in the procedure employed by the Canadian Agency for Drugs and Technologies in Health (CADTH) in this project were topic identification and scoping; evidence synthesis (i.e., systematic review) and cost analysis; development of optimal use recommendations by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee (CERC); and development and dissemination of implementation tools to promote uptake of the recommendations. A broad range of stakeholders were invited to provide feedback at key stages in the process.

COMPUS Expert Review Committee Process

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office and three or more Specialist Experts appointed to provide their expertise in recommending optimal use for one or more specific topics. For topics in the area of mental health, four specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members are physicians or pharmacists with expertise in pharmacotherapy and critical appraisal of evidence. The Core Members including Public Members were appointed by the CADTH Board of Directors. The mandate of CERC is advisory in nature and consists of providing recommendations and advice to CADTH on assigned topics relating to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada.

A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used by CERC to develop the recommendations. Deliberations occurred by teleconference and at an in-person meeting. Recommendations were voted upon by Committee members, and considered passed if a majority voted in favour. Committee members also voted on the overall quality of evidence (i.e., high, moderate, or low) available for each recommendation. (Quorum consisted of a minimum of five core CERC members and 50% of the committee members appointed as clinical experts in the management of schizophrenia.) In addition, the Committee identified the main values and preferences underlying the recommendation. Draft recommendations were posted on the CADTH website to elicit stakeholder feedback, which was considered by CERC before recommendations were finalized. More details regarding the CERC process can be found in the project protocol (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A cost-effectiveness analysis based upon the results of the systematic review was originally planned. However, in consultation with the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee (CERC), it was determined that such an analysis would be of limited utility, given the lack of consistent differences in efficacy and safety between high-dose and combination treatment strategies and standard-dose antipsychotic monotherapy. Hence, the cost information provided for CERC's deliberations consisted of the acquisition costs for the various treatment strategies considered (see Appendix 3 of the original guideline document).

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

A broad range of stakeholders are invited to provide feedback at key stages in the Canadian Agency for Drugs and Technologies in Health (CADTH) process.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The recommendations are based on clinical evidence (chiefly randomized controlled trials), economic evidence, and values and preferences.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Optimal use of atypical antipsychotic (AAP) treatment strategies in adolescents and adults with schizophrenia
- Improved patient outcomes
- Avoidance of adverse effects of high-dose and combination therapy with AAPs
- Improved cost-effectiveness of therapy

Potential Harms

Adverse effects of recommended treatments, including agranulocytosis, changes in cholesterol, extrapyramidal symptoms, mortality, Parkinsonism, suicide, suicide ideation, weight gain, and withdrawals.

Qualifying Statements

Qualifying Statements

- The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While the Canadian Agency for Drugs and Technologies in Health (CADTH) has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or

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- CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

Implementation of the Guideline

Description of Implementation Strategy

Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee (CERC) Process and Perspective

CERC develops recommendations and advice with the aim of contributing to optimal health outcomes and fostering a sustainable health care system for Canadians. CERC considers the practical needs of policy-makers, health care providers, and consumers in implementing and using the recommendations and advice toward the promotion of optimal practices. To assist in knowledge transfer to intended audiences, CERC also develops Context Statements (where appropriate) to provide guidance based on clinical judgment where there is insufficient evidence, and to provide commentary relating to the evidence.

Next Steps

The Optimal Use Recommendations will be widely disseminated to encourage uptake and implementation by decision-makers at various levels (e.g., policy decision-makers, health care professionals, and patients). Gaps in practice and knowledge related to the use of atypical antipsychotic drugs will be identified by comparing the final recommendations with information on current practice and utilization of these products in Canada.

Key messages to promote the optimal prescribing and use of atypical antipsychotics will be developed to address identified gaps in practice and knowledge. Intervention tools will be populated with the key messages and related evidence for implementation across Canada.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Canadian Agency for Drugs and Technologies in Health (CADTH). Optimal use recommendations for atypical antipsychotics: combination and high-dose treatment strategies in adolescents and adults with schizophrenia. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2011 Dec. 30 p. [50 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Dec

Guideline Developer(s)

Canadian Agency for Drugs and Technologies in Health - Nonprofit Organization

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Guideline Committee

Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee (CERC)

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Financial Disclosures/Conflicts of Interest

Conflicts of Interest

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Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Canadian Agency for Drugs and Technologies in Health (CADTH) Web site .

Availability of Companion Documents

The following are available:

- A systematic review of combination and high dose atypical antipsychotic therapy in patients with schizophrenia. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2011 Aug. 207 p. Electronic copies: Available in Portable Document Format (PDF) from the Canadian Agency for Drugs and Technologies in Health (CADTH) Web site .
- Current practice study: atypical antipsychotic agents for patients with schizophrenia. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2012 Aug. 46 p. Electronic copies: Available in PDF from the CADTH Web site .
- Current utilization of antipsychotic agents for schizophrenia: combination and high dose therapies. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2012 Aug. 35 p. Electronic copies: Available in PDF from the CADTH Web site .
- Atypical antipsychotics for schizophrenia: combination therapy and high doses. Project protocol. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2011 Aug. 54 p. Electronic copies: Available in PDF from the CADTH Web site .
- Atypical antipsychotics for schizophrenia: combination therapy and high doses. Summary with action plan. 1 p. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2011. Electronic copies: Available in PDF from the CADTH Web site .
- Atypical antipsychotics for schizophrenia: combination therapy and high doses. Project in brief. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2011 Dec. 1 p. Electronic copies: Available in PDF from the CADTH Web site .

Patient Resources

None available

NGC Status

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